Please add new claims 9-11.

9. (New) A composition according to any one of claims 1-8 wherein the cell surface receptor antigen is Her2/Neu, the first immune response altering molecule is 4-1BB ligand, and the second immune response altering molecule is CD86/B7.2.

10. (New) The composition of claim 9 wherein Her2/Neu comprises a polypeptide sequence selected from the group consisting of sequences set forth in GenBank Acc. Nos. X03363, M17730, and SEG_HUMHER20.

11. (New) The composition of claim 9 wherein CD86/B7.2 comprises a polypeptide sequence selected from the group consisting of sequences set forth in GenBank Acc. Nos. AF099105, SEG_MMB72G, U39466, U04343, SEG_HSB725, L25606, and L25259.

REMARKS

Reconsideration of the present application is respectfully requested in view of the following remarks. Claims 1-8 were pending. Claims 9-11 have been added. Accordingly, claims 1-11 are pending. Support for claim 9 may be found, for example, at page 8, line 27, page 13, line 21, page 15, line 22, and Examples 1-5. Support for claim 10 may be found, for example, at page 8, lines 27-29. Support for claim 11 may be found, for example at page 13, lines 21-24. Claims 1-8 have been amended to more specifically define certain aspects of the present invention, without acquiescing to the assertions in the Action. Support for the term "composition" in claims 1-8 may be found in the specification, for example, at page 3, lines 8-10. Support for the phrase "wherein said first immune response altering molecule is a T cell agent" in claims 2, 4, 6 and 8 may be found in the specification, for example, at page 11, lines 10-13. No new matter has been added.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

The Examiner has maintained the rejection of claims 1-8 for alleged lack of enabling support in the specification. In particular, the Action acknowledges that the specification enables a vaccine for eliciting or enhancing the titer of antibodies specific for Her2/neu protein, wherein the vaccine comprises individual expression constructs that recombinantly express Her2/neu, murine B7.2, or 4-1Bb ligand. The Examiner asserts, however, that the scope of the disclosure is not commensurate with the scope of *any* vaccine for enhancing or eliciting the titer of antibodies for *any* cell surface receptor antigen, according to the claims. Again citing Eck (1996) and also citing Verma et al. (1997 *Nature* 389:239), the Examiner asserts further that numerous factors may complicate gene therapy in a manner that cannot be overcome by routine experimentation, when allegedly, delivery and expression of a gene in a manner appropriate to elicit the desired (antibody) response cannot be performed in a particular fashion.

Applicants respectfully traverse these grounds for rejection and submit that the present application satisfies the requirements of 35 U.S.C. § 112, first paragraph. The present invention is directed in pertinent part to a composition for eliciting or enhancing the titer of antibodies specific for a cell surface receptor, comprising one or more recombination expression constructs comprising at least one promoter operably linked to a nucleic acid sequence encoding a cell surface receptor antigen (SRA) and at a first and a second immune response altering molecule (IRAM). The Action inappropriately focuses on predictability of the invention and asserts that the art is too unpredictable to enable the invention as claimed. Enablement, however, is a "conclusion reached by weighing many factual considerations." *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988).

The Action specifically asserts that gene delivery and assessment of the *in vivo* effects of a gene once delivered are inadequately disclosed. Applicants submit that the state of the art, the relative skill of those in the art, and the guidance presented in the instant specification enable the claimed composition. *See In re Wands*, 858 F.2d at 737, 8 U.S.P.Q.2d 1400 (stating that undue experimentation is not determined by a single factual determination but is concluded "by weighing many factual considerations). At the time of filing of the instant application, DNA

constructs were successfully used to elicit protective antibody and cell-mediated immune responses. *See* J.J. Donnelly et al., 1997 *Annu. Rev. Immunol.* 15:617, 617 (DNA immunization has been used to elicit protective antibody and cell-mediated immune responses in a wide variety of pre-clinical animal models.). *See id.* at 620 ("The remarkable number of publications demonstrating efficacy of DNA vaccines in various pre-clinical models that have appeared since the publication of the initial demonstration of the generation of protective efficacy attest to the simplicity as well as the robustness of the technology."). For example, a T cell response to tumor antigens was stimulated by administering recombinant poxvirus vaccines encoding T cell accessory molecules. J. Schlom et al., 1999 *Immunol. Rev.* 170:73. Human clinical trials of vaccines for the treatment of acquired disorders, such as AIDS and cancer, have proceeded more rapidly than those for treatment of single-gene defects. Eck et al., 1996, page 78. Eck notes that adding a new molecular function or blocking an existing function in an acquired disease is more easily accomplished than correcting an underlying deficiency as in genetic diseases. *See id.*

Applicants respectfully submit that the results of the mouse tumor model demonstrate that one skilled in the art could make and use the invention as claimed. Applicants disagree with the Examiner that understanding parameters such as the level and location of gene expression, the fate of the DNA vector, and trafficking of the DNA, and other parameters listed by Eck et al. render the Applicants' invention unpredictable. Such parameters may increase the understanding of how the DNA molecule works, but none are essential to the subject matter of the invention. Applicants disclose and claim a DNA composition that enhances and elicits an antibody response to a cell surface antigen and that impairs tumor growth in animals, which claimed DNA composition is therefore readily enabled without analyzing its expression or fate. The above parameters may have relevance to studies undertaken in clinical research and development for testing the safety and efficacy of a compound. Applicants respectfully submit, however, that such studies are beyond the requirements for patentability. *See Scott v. Finney*, 34 F.3d 1058, 1063-64, 32 U.S.P.Q.2d 1115 (Fed. Cir. 1994) (ruling that testing for safety and effectiveness is properly left to the FDA).

Unexpectedly, and as described in the instant specification, the composition of the present invention, comprising recombinant expression construct(s) encoding an SRA and a first

and a second IRAM, elicited and enhanced a *humoral* (*i.e.*, antibody) response to the SRA rather than solely stimulating a T cell (*i.e.*, cell-mediated) response. Moreover, the composition induced high and sustained antibody titers in a host that would otherwise be incapable of generating an antibody response, or would only generate a far weaker response. *See* Specification, page 6, lines 26-30. Other means of stimulating or enhancing a humoral response to an antigen are known to those skilled in the art, and are not exclusively restricted in their applicability only to single antigens. For example, methods such as co-injection with Freund's adjuvant or conjugation to a carrier protein are applicable to multiple antigens. Therefore, by analogy, one skilled in the art would, based on the teachings of the present application, expect that the claimed composition comprising a nucleic acid sequence encoding an SRA other than the representative cell surface receptor antigen provided in the working example would elicit an antibody response. Applicants respectfully submit that extending the teachings in the present specification to other SRA molecules is a matter of routine experimentation, including insertion of a nucleic acid sequence encoding an SRA into a recited expression construct and determination of a *humoral* immune response in a host, by methods known in the art and described in the present specification. Thus, those skilled in the art could readily and without undue experimentation realize the effect of interchanging an SRA according to the instant claims. The constitutional purpose of promoting progress in the useful arts would not be served by demanding that the first to disclose an invention "shall limit his claims to what he has found will work or to materials which meet the guidelines specified for 'preferred' materials in a process." *In re Goffe*, 542 F.2d 564, 567, 191 U.S.P.Q. 429, 431 (CCPA 1976).

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version With Markings to Show Changes Made**."

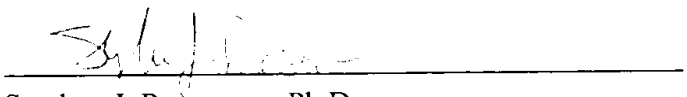
Applicants respectfully submit that claims 1-8 are enabled and request that rejection of the claims be withdrawn. In view of the above remarks, Applicants submit that the

claims are now in condition for allowance and respectfully request that a Notice be issued to that effect.

Respectfully submitted,

Nathalie B. Scholler et al.

Seed Intellectual Property Law Group PLLC



Stephen J. Rosenman, Ph.D.
Registration No. 43,058

QXL:jab

Enclosures:

- Postcard
- Check
- Form PTO/SB/21
- Form PTO/SB/17 (+ copy)
- Petition for an Extension of Time
- Request for Continued Examination

701 Fifth Avenue, Suite 6300
Seattle, Washington 98104-7092
Phone: (206) 622-4900
Fax: (206) 682-6031

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 1-8 have been amended as follows:

1. (Twice Amended) A composition ~~cell surface receptor antigen vaccine~~ for eliciting or enhancing the titer of antibodies specific for a cell surface receptor antigen, comprising:

a recombinant expression construct comprising at least one promoter operably linked to a nucleic acid sequence encoding a cell surface receptor antigen, a nucleic acid sequence encoding a first immune response altering molecule and a nucleic acid sequence encoding a second immune response altering molecule, wherein said first and second immune response altering molecules are different from each other and are selected from the group consisting of an accessory cell agent and a T cell agent.

2. (Twice Amended) A composition ~~cell surface receptor antigen vaccine~~ for eliciting or enhancing the titer of antibodies specific for a cell surface receptor antigen, comprising the expression products of the recombinant expression construct according to claim 1, wherein said first immune response altering molecule is a T cell agent.

3. (Twice Amended) A composition ~~cell surface receptor antigen vaccine~~ for eliciting or enhancing the titer of antibodies specific for a cell surface receptor antigen, comprising:

a) a first recombinant expression construct containing at least one promoter operably linked to a nucleic acid sequence encoding a cell surface receptor antigen and a nucleic acid sequence encoding a first immune response altering molecule; and

b) a second recombinant expression construct containing a promoter operably linked to a nucleic acid sequence encoding a second immune response altering molecule,

wherein said first and second immune response altering molecules are different from each other and are selected from the group consisting of an accessory cell agent and a T cell agent.

4. (Twice Amended) A composition ~~cell surface receptor antigen vaccine~~ for eliciting or enhancing the titer of antibodies specific for a cell surface receptor antigen, comprising the expression products of the recombinant constructs according to claim 3, wherein said first immune response altering molecule is a T cell agent.

5. (Twice Amended) A composition ~~cell surface receptor antigen vaccine~~ for eliciting or enhancing the titer of antibodies specific for a cell surface receptor antigen, comprising:

a) a first recombinant expression construct containing at least one promoter operably linked to a nucleic acid sequence encoding a cell surface receptor antigen;

b) a second recombinant expression construct containing a promoter operably linked to a nucleic acid sequence encoding a first immune response altering molecule; and

c) a third recombinant expression construct containing a promoter operably linked to a nucleic acid sequence encoding a second immune response altering molecule,

wherein said first and second immune response altering molecules are different from each other and are selected from the group consisting of an accessory cell agent and a T cell agent.

6. (Twice Amended) A composition ~~cell surface receptor antigen vaccine~~ for eliciting or enhancing the titer of antibodies specific for a cell surface receptor antigen, comprising the expression products of the recombinant expression constructs according to claim 5, wherein said first immune response altering molecule is a T cell agent.

7. (Twice Amended) A composition ~~cell surface receptor antigen vaccine~~ for eliciting or enhancing the titer of antibodies specific for a cell surface receptor antigen, comprising:

a) a first recombinant expression construct containing at least one promoter operably linked to a nucleic acid sequence encoding a cell surface receptor antigen; and

b) a second recombinant expression construct containing at least one promoter operably linked to a nucleic acid sequence encoding a first immune response altering molecule and a nucleic acid sequence encoding a second immune response altering molecule, wherein said first and second immune response altering molecules are different from each other and are selected from the group consisting of an accessory cell agent and a T cell agent.

8. (Twice Amended) A composition ~~cell surface receptor antigen vaccine~~ for eliciting or enhancing the titer of antibodies specific for a cell surface receptor antigen, comprising the expression products of the recombinant expression constructs according to claim 7, wherein said first immune response altering molecule is a T cell agent.

New claims 9-11 have been added as follows:

9. (New) A composition according to any one of claims 1-8 wherein the cell surface receptor antigen is Her2/Neu, the first immune response altering molecule is 4-1BB ligand, and the second immune response altering molecule is CD86/B7.2.

10. (New) The composition of claim 9 wherein Her2/Neu comprises a polypeptide sequence selected from the group consisting of sequences set forth in GenBank Acc. Nos. X03363, M17730, and SEG_HUMHER20.

11. (New) The composition of claim 9 wherein CD86/B7.2 comprises a polypeptide sequence selected from the group consisting of sequences set forth in GenBank Acc. Nos. AF099105, SEG_MMB72G, U39466, U04343, SEG_HSB725, L25606, and L25259.